National Institute on Drug Abuse (NIDA)

Methamphetamine

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Overview

The misuse of methamphetamine—a potent and highly addictive stimulant—remains an extremely serious problem in the United States. In some areas of the country, it poses an even greater threat than opioids, and it is the drug that most contributes to violent crime.[36] According to data from the 2017 National Survey on Drug Use and Health (NSDUH), over 14.7 million people (5.4 percent of the population) have tried methamphetamine at least once. NSDUH also reports that almost 1.6 million people used methamphetamine in the year leading up to the survey,[1] and it remains one of the most commonly misused stimulant drugs in the world.[37]

The consequences of methamphetamine misuse are terrible for the individual—psychologically, medically, and socially. Using the drug can cause memory loss, aggression, psychotic behavior, damage to the cardiovascular system, malnutrition, and severe dental problems. Methamphetamine misuse has also been shown to contribute to increased transmission of infectious diseases, such as hepatitis and HIV/AIDS.

Beyond its devastating effects on individual health, methamphetamine misuse threatens whole communities, causing new waves of crime, unemployment, child neglect or abuse, and other social ills. A 2009 report from the RAND Corporation noted that methamphetamine misuse cost the nation approximately $23.4 billion in 2005.[1]

But the good news is that methamphetamine misuse can be prevented and addiction to the drug can be treated with behavioral therapies. Research also continues toward development of new pharmacological and other treatments for methamphetamine use, including medications, vaccines, and noninvasive stimulation of the brain using magnetic fields. People can and do recover from methamphetamine addiction if they have ready access to effective treatments that address the multitude of medical and personal problems resulting from

their long-term use of the drug.

What is methamphetamine?

Photo by DEA
Crystal methamphetamine

Methamphetamine is a powerful, highly addictive stimulant that affects the central nervous system. Also known as meth, blue, ice, and crystal, among many other terms, it takes the form of a white, odorless, bitter-tasting crystalline powder that easily dissolves in water or alcohol.[36,37]

Methamphetamine was developed early in the 20th century from its parent drug, amphetamine, and was used originally in nasal decongestants and bronchial inhalers. Like amphetamine, methamphetamine causes increased activity and talkativeness, decreased appetite, and a pleasurable sense of well-being or euphoria. However, methamphetamine differs from amphetamine in that, at comparable doses, much greater amounts of the drug get into the brain, making it a more potent stimulant.[38] It also has longer-lasting and more harmful effects on the central nervous system.[39] These characteristics make it a drug with high potential for widespread

misuse.

Methamphetamine has been classified by the U.S. Drug Enforcement Administration as a Schedule II stimulant, which makes it legally available only through a nonrefillable prescription. Medically it may be indicated for the treatment of attention deficit hyperactivity disorder (ADHD) and as a short-term component of weight-loss treatments, but these uses are limited and it is rarely prescribed; also, the prescribed doses are far lower than those typically misused.[40]

What is the scope of methamphetamine misuse in the United States?

According to the 2017 National Survey on Drug Use and Health (NSDUH), approximately 1.6 million people (0.6 percent of the population) reported using methamphetamine in the past year, and 774,000 (0.3 percent) reported using it in the past month. The average age of new methamphetamine users in 2016 was 23.3 years old.[2]

An estimated 964,000 people aged 12 or older (about 0.4 percent of the population) had a methamphetamine use disorder in 2017—that is, they reported clinically significant impairment, including health problems, disability, and failure to meet responsibilities at work, school, or home as a result of their drug use. This number is significantly higher than the 684,000 people who reported having methamphetamine use disorder in 2016.

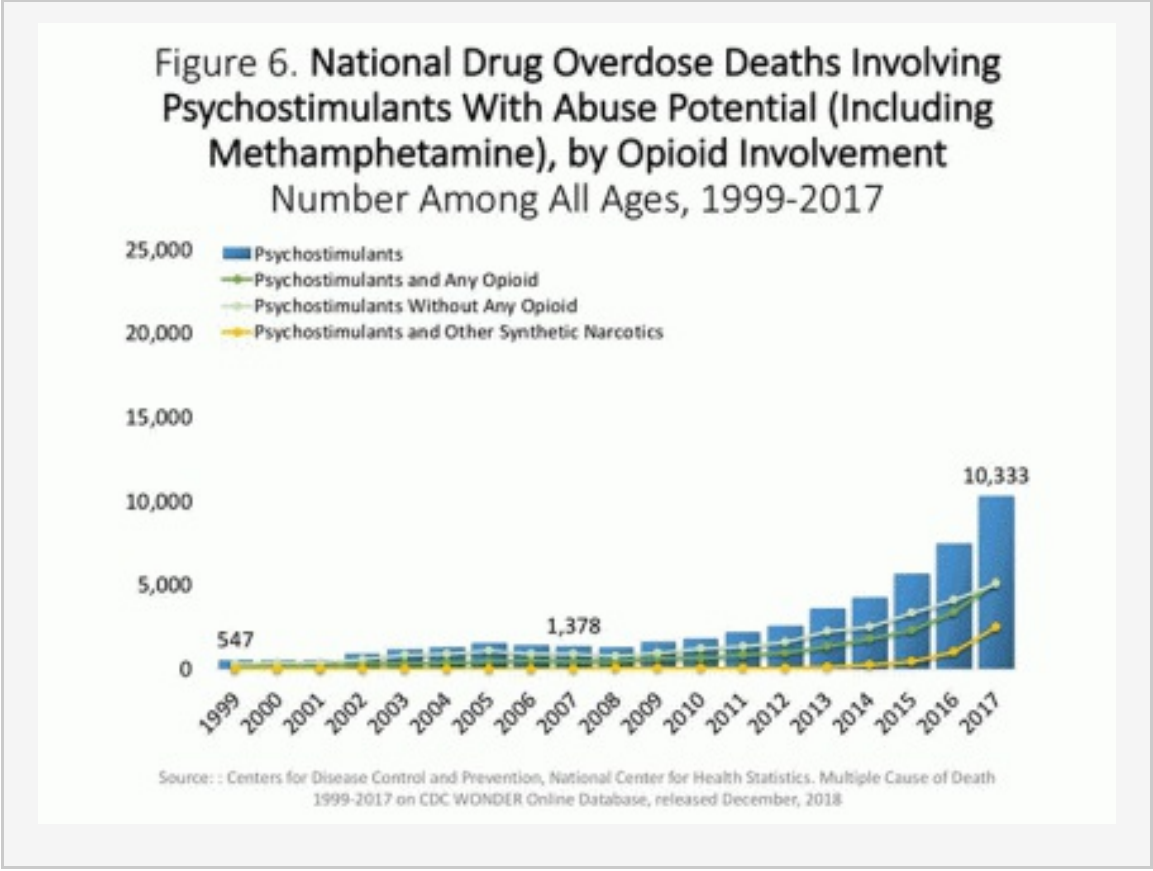
The 2018 Monitoring the Future (MTF) survey of adolescent drug use and attitudes reported that about 0.5 percent of 8th, 10th, and 12th graders had used methamphetamine within the past year. Use of methamphetamine by adolescents has declined significantly since 1999, when this drug was first added to the survey.[3]

The Treatment Episode Data Set (TEDS) provides information on admissions to substance abuse treatment facilities that are licensed or certified by state substance use agencies. According to TEDS data, nationwide treatment admissions for methamphetamine misuse dropped from 68 per 100,000 individuals in 2005 to 49 per 100,000 in 2015.[39]

An important caveat to these national numbers is the degree to which they mask regional variability. While methamphetamine is available

across the US, highest availability is in the western and midwestern regions of the US; more than 70 percent of local law enforcement agencies from the pacific and west central regions of the US report methamphetamine as the greatest drug threat in their area.[41]

NIDA's National Drug Early Warning System (NDEWS), which tracks drug trends in sentinel sites across the country, found that treatment admissions for methamphetamine as the primary substance of use were less than one percent in sites east of the Mississippi River, but ranged from 12-29 percent in the sites west of the Mississippi.[41] Nationwide, overdose deaths from the category of drugs that includes methamphetamine increased by 7.5 times between 2007 and 2017. About 15 percent of all drug overdose deaths involved the methamphetamine category in 2017, and 50 percent of those deaths also involved an opioid.[42] In 2017, 5 of the 12 NDEWS sites reported increases in methamphetamine overdose deaths: Washington, Colorado, Texas, Florida, and Georgia.[41]



How is methamphetamine misused?

Methamphetamine comes in several forms and can be smoked, snorted, injected, or orally ingested. The preferred method of using the drug varies by geographical region and has changed over time.[37,38,43]

Smoking or injecting methamphetamine puts the drug very quickly into the bloodstream and brain, causing an immediate, intense "rush" and amplifying the drug's addiction potential and adverse health consequences. The rush, or "flash," lasts only a few minutes and is described as extremely pleasurable. Snorting or oral ingestion produces euphoria—a high, but not an intense rush. Snorting produces effects within 3 to 5 minutes, and oral ingestion produces effects within 15 to 20 minutes.[4]

As with many stimulants, methamphetamine is most often misused in a "binge and crash" pattern. Because the pleasurable effects of methamphetamine disappear even before the drug concentration in the blood falls significantly, users try to maintain the high by taking more of the drug. In some cases, people indulge in a form of binging known as a "run," foregoing food and sleep while continuing to take the drug for up to several days.[37,38,43]

How is methamphetamine manufactured?

Currently, most methamphetamine in the United States is produced by transnational criminal organizations (TCOs) in Mexico.[44] This methamphetamine is highly pure, potent, and low in price. The drug can be easily made in small clandestine laboratories, with relatively inexpensive over-the-counter ingredients such as pseudoephedrine, a common ingredient in cold medications.

To curb production of methamphetamine, Congress passed the Combat Methamphetamine Epidemic Act in 2005, which requires that pharmacies and other retail stores keep logs of purchases of products containing pseudoephedrine and limits the amount of those products an individual can purchase per day. Restrictions on the chemicals used to make methamphetamine in the United States have dramatically reduced domestic production of the drug. In 2010, there were 15,256 domestic methamphetamine laboratory incidents—a figure that has fallen over 80 percent to 3,036 in 2017.[44] Data on drug seizures indicate that most domestic production of methamphetamine is now conducted in small laboratories that make two ounces or less of the drug using common household items.[44]

Mexico has also tightened its restrictions on pseudoephedrine and other methamphetamine precursor chemicals. But manufacturers adapt to these restrictions via small- or large-scale "smurfing" operations: obtaining pseudoephedrine from multiple sources, below the legal thresholds, using multiple false identifications. Manufacturers in Mexico are also increasingly using a different production process (called P2P which stands for pseudoephedrine's precursor chemical, phenyl-2-propanone) to make methamphetamine that does not require pseudoephedrine.

When methamphetamine is smuggled into the United States in powder or liquid form, domestic conversion laboratories transform it into

crystal methamphetamine. These laboratories do not require a significant amount of equipment, so they can be small in size and thus easily concealed, which presents challenges to law enforcement agencies.[44] Methamphetamine pressed into a pill form intended to resemble ecstasy has also recently emerged, potentially in an effort to make methamphetamine more appealing to people who haven't tried it before.[44] As with other illicit drugs like heroin and cocaine, methamphetamine is also sometimes laced with fentanyl.[44]

Methamphetamine production is also an environmental concern; it involves many easily obtained chemicals that are hazardous, such as acetone, anhydrous ammonia (fertilizer), ether, red phosphorus, and lithium. Toxicity from these chemicals can remain in the environment around a methamphetamine production lab long after the lab has been shut down, causing a wide range of damaging effects to health. Because of these dangers, the U.S. Environmental Protection Agency has provided guidance on cleanup and remediation of methamphetamine labs.

How is methamphetamine different from other stimulants, such as cocaine?

The methamphetamine molecule is structurally similar to amphetamine and to the neurotransmitter dopamine, a brain chemical that plays an important role in the reinforcement of rewarding behaviors, but it is quite different from cocaine.[45] Although these stimulants have similar behavioral and physiological effects, there are some major differences in the basic mechanisms of how they work.

In contrast to cocaine, which is quickly removed from and almost completely metabolized in the body, methamphetamine has a much longer duration of action, and a larger percentage of the drug remains unchanged in the body. Methamphetamine therefore remains in the brain longer, which ultimately leads to prolonged stimulant effects.[46]

Although both methamphetamine and cocaine increase levels of dopamine, administration of methamphetamine in animal studies leads to much higher levels of dopamine, because nerve cells respond differently to the two drugs. Cocaine prolongs dopamine actions in the brain by blocking the re-absorption (re-uptake) of the neurotransmitter by signaling nerve cells. At low doses, methamphetamine also blocks the re-uptake of dopamine, but it also increases the release of dopamine, leading to much higher concentrations in the synapse (the gap between neurons), which can be toxic to nerve terminals.[38,39]

Methamphetamine versus Cocaine

Methamphetamine	Cocaine
Stimulant	Stimulant and local anesthetic
Man-made	Plant-derived
Smoking produces a long-lasting high	Smoking produces a brief high
50% of the drug is removed from the body in 12 hours	50% of the drug is removed from the body in 1 hour
Increases dopamine release and blocks dopamine re-uptake	Blocks dopamine re-uptake
Limited medical use for ADHD, narcolepsy, and weight loss	Limited medical use as a local anesthetic in some surgical procedures

What are the immediate (short-term) effects of methamphetamine misuse?

As a powerful stimulant, methamphetamine, even in small doses, can increase wakefulness and physical activity and decrease appetite. Methamphetamine can also cause a variety of cardiovascular problems, including rapid heart rate, irregular heartbeat, and increased blood pressure. Hyperthermia (elevated body temperature) and convulsions may occur with methamphetamine overdose, and if not treated immediately, can result in death.[37,38]

The exact mechanisms whereby drugs like methamphetamine produce euphoria (the pleasurable high) are still poorly understood. But along with euphoria, methamphetamine use releases very high levels of the neurotransmitter dopamine in the reward circuit, which "teaches" the brain to repeat the pleasurable activity of taking the drug. Dopamine is involved in motivation and motor function and its release in the reward circuit is a defining feature of addictive drugs. The elevated release of dopamine produced by methamphetamine is also thought to contribute to the drug's deleterious effects on nerve terminals in the brain.

Short-term effects may include:

- increased attention and decreased fatigue
- increased activity and wakefulness
- decreased appetite
- euphoria and rush
- increased respiration
- rapid/irregular heartbeat
- hyperthermia

What are the long-term effects of methamphetamine misuse?

Long-term methamphetamine abuse has many negative consequences, including addiction. Addiction is a chronic, relapsing disease, characterized by compulsive drug seeking and use and accompanied by functional and molecular changes in the brain.

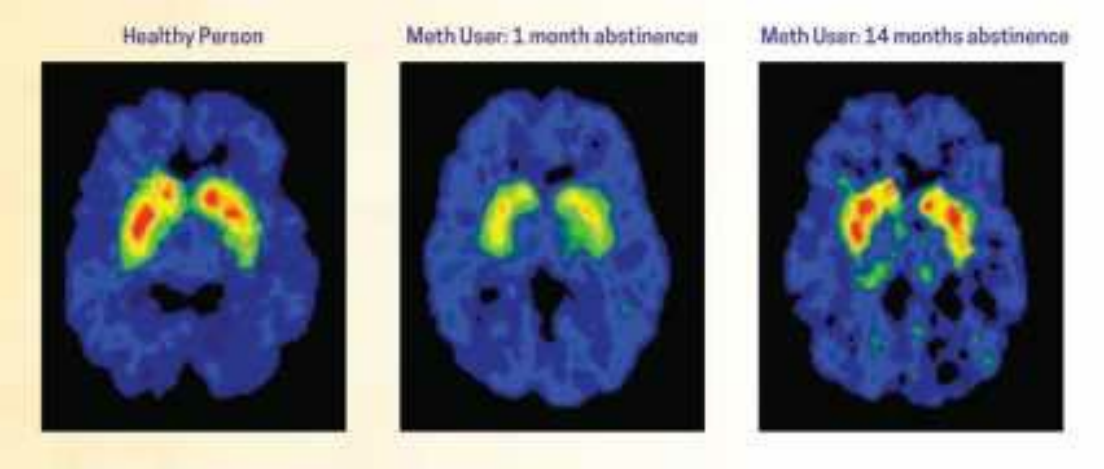
As is the case with many drugs, tolerance to methamphetamine's pleasurable effects develops when it is taken repeatedly. Abusers often need to take higher doses of the drug, take it more frequently, or change how they take it in an effort to get the desired effect. Chronic methamphetamine abusers may develop difficulty feeling any pleasure other than that provided by the drug, fueling further abuse. Withdrawal from methamphetamine occurs when a chronic abuser stops taking the drug; symptoms of withdrawal include depression, anxiety, fatigue, and an intense craving for the drug.[43]

In addition to being addicted to methamphetamine, chronic abusers may exhibit symptoms that can include significant anxiety, confusion, insomnia, mood disturbances, and violent behavior.[47] They also may display a number of psychotic features, including paranoia, visual and auditory hallucinations, and delusions (for example, the sensation of insects creeping under the skin).[48] Psychotic symptoms can sometimes last for months or years after a person has quit abusing methamphetamine, and stress has been shown to precipitate spontaneous recurrence of methamphetamine psychosis in formerly psychotic methamphetamine abusers.[49]

These and other problems reflect significant changes in the brain caused by misuse of methamphetamine. Neuroimaging studies have demonstrated alterations in the activity of the dopamine system that are associated with reduced motor speed and impaired verbal learning.[6,7,8] Studies in chronic methamphetamine users have also revealed severe structural and functional changes in areas of the brain

associated with emotion and memory, which may account for many of the emotional and cognitive problems observed in these individuals.[9,10,11]

Research in primate models has found that methamphetamine alters brain structures involved in decision-making and impairs the ability to suppress habitual behaviors that have become useless or counterproductive. The two effects were correlated, suggesting that the structural change underlies the decline in mental flexibility.[12] These changes in brain structure and function could explain why methamphetamine addiction is so hard to treat and has a significant chance of relapse early in treatment.



Recovery of Brain Dopamine Transporters in Chronic Methamphetamine (METH) Users
Methamphetamine misuse greatly reduces the binding of dopamine to dopamine transporters (highlighted in red and green) in the striatum, a brain area important in memory and movement. With prolonged abstinence, dopamine transporters in this area can be restored.

Methamphetamine misuse also has been shown to have negative effects on non-neural brain cells called microglia. These cells support brain health by defending the brain against infectious agents and removing damaged neurons. Too much activity of the microglial cells, however, can assault healthy neurons. A study using brain imaging found more than double the levels of microglial cells in people who previously misused methamphetamine compared to people with no

history of methamphetamine misuse, which could explain some of the neurotoxic effects of methamphetamine.[13]

Some of the neurobiological effects of chronic methamphetamine misuse appear to be, at least, partially reversible. In the study just mentioned, abstinence from methamphetamine resulted in less excess microglial activation over time, and users who had remained methamphetamine-free for 2 years exhibited microglial activation levels similar to the study's control subjects.[14] A similar study found that while biochemical markers for nerve damage and viability persist in the brain through 6 months of abstinence from methamphetamine, those markers return to normal after a year or more without taking the drug.[15] Another neuroimaging study showed neuronal recovery in some brain regions following prolonged abstinence (14 but not 6 months).[16] This recovery was associated with improved performance on motor and verbal memory tests. Function in other brain regions did not recover even after 14 months of abstinence, indicating that some methamphetamine-induced changes are very long lasting. Methamphetamine use can also increase one's risk of stroke, which can cause irreversible damage to the brain. A recent study even showed higher incidence of Parkinson's disease among past users of methamphetamine.[17]

In addition to the neurological and behavioral consequences of methamphetamine misuse, long-term users also suffer physical effects, including weight loss, severe tooth decay and tooth loss ("meth mouth"), and skin sores.[38] The dental problems may be caused by a combination of poor nutrition and dental hygiene as well as dry mouth and teeth grinding caused by the drug. Skin sores are the result of picking and scratching the skin to get rid of insects imagined to be crawling under it.[38]

Long-term effects may include:

- addiction
- psychosis, including:
  - paranoia
  - hallucinations
  - repetitive motor activity
- changes in brain structure and function
- deficits in thinking and motor skills
- increased distractibility
- memory loss
- aggressive or violent behavior
- mood disturbances
- severe dental problems
- weight loss

What are the risks of methamphetamine misuse during pregnancy?

Our knowledge of the effects of methamphetamine misuse during pregnancy is limited because studies of this issue have used small samples and did not account for other possible drug use besides methamphetamine in research samples. But the available research indicates increased rates of premature delivery, placental abruption (separation of the placental lining from the uterus), and various effects on babies prenatally exposed to methamphetamine, including small size, lethargy, and heart and brain abnormalities.[18,19]

A large NIDA-funded prospective, longitudinal study examined developmental outcomes in infants and children born to mothers who misused methamphetamine. In infancy, they were more likely to show decreased arousal, increased stress, and poor quality of movement.[20,21] By ages 1 and 2, toddlers showed delayed motor development.[22] Preschool and school-age children had subtle but significant attention impairments and were more likely to have cognitive and behavioral issues in school related to difficulties with self-control and executive function.[22,23,24,25,26,27]

Are people who misuse methamphetamine at risk for contracting HIV/AIDS and hepatitis B and C?

Methamphetamine misuse raises the risk of contracting or transmitting HIV and hepatitis B and C—not only for individuals who inject the drug but also for noninjecting methamphetamine users. Among people who inject drugs, HIV and other infectious diseases are spread primarily through the re-use or sharing of contaminated syringes, needles, or related paraphernalia. But regardless of how methamphetamine is taken, its strong effects can alter judgment and inhibition and lead people to engage in risky behaviors like unprotected sex.

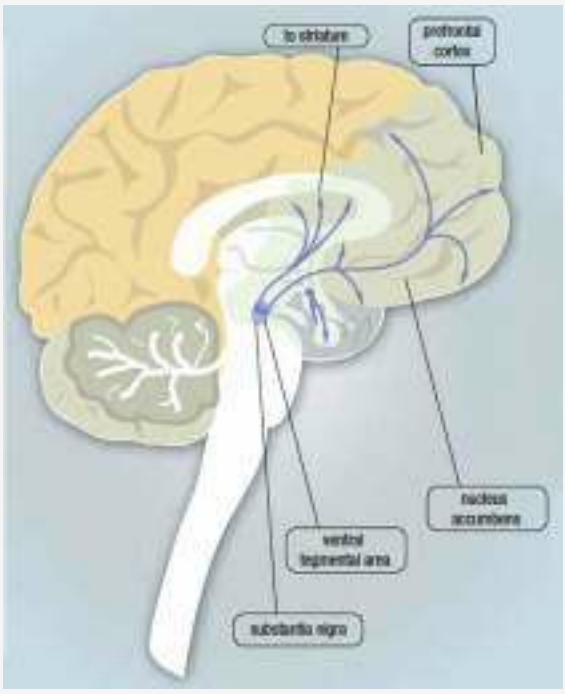
Methamphetamine misuse is associated with a culture of risky sexual behavior, both among men who have sex with men and in heterosexual populations, a link that may be attributed to the fact that methamphetamine and related stimulants can increase libido. (However, long-term methamphetamine misuse may be associated with decreased sexual functioning, at least in men.) The combination of injection practices and sexual risk-taking may result in HIV becoming a greater problem among people who misuse methamphetamine than among other drug users, and some epidemiologic reports are already showing this trend. For example, while the link between HIV infection and methamphetamine misuse has not yet been established for heterosexuals, data show an association between methamphetamine misuse and the spread of HIV among men who have sex with men.

Methamphetamine misuse may also worsen the progression of HIV disease and its consequences. In animal studies, methamphetamine has been shown to increase viral replication.[27] Clinical studies in humans suggest that current methamphetamine users taking highly active antiretroviral therapy (HAART) to treat HIV may be at greater

risk of developing AIDS than non-users, possibly because of poor medication adherence.[28,29] Methamphetamine users with HIV also have shown greater neuronal injury and cognitive impairment due to HIV, compared with those who do not misuse the drug.[30, 31, 32]

NIDA-funded research has found that, through substance use disorder treatment, prevention, and community-based outreach programs, drug users can change their HIV risk behaviors. Drug misuse and drug-related risk behaviors, such as needle sharing and risky sexual practices, can be reduced significantly, thus decreasing the risk of exposure to HIV and other infectious diseases. Therefore, drug treatment is HIV prevention.

Dopamine Pathways



In the brain, dopamine plays an important role in both movement and the reinforcement of rewarding behaviors. As a major chemical messenger in the reward pathway, dopamine is manufactured in nerve cell bodies located within a group of neurons called the ventral tegmental area and is released in the nucleus accumbens, which is a key brain region for learning to repeat pleasurable activities, as well as in the prefrontal cortex, which is responsible for higher cognitive functions like decision-making and self-control. Dopamine's regulation of motor functions is linked to a separate pathway: Cell bodies in the substantia nigra manufacture and release dopamine into the striatum, which is involved in executing and inhibiting movements and reward-seeking behavior.

What treatments are effective for people who misuse methamphetamine?

The most effective treatments for methamphetamine addiction at this point are behavioral therapies, such as cognitive-behavioral and contingency management interventions. For example, the Matrix Model—a 16-week comprehensive behavioral treatment approach that combines behavioral therapy, family education, individual counseling, 12-step support, drug testing, and encouragement for non-drug-related activities—has been shown to be effective in reducing methamphetamine misuse.[33,34] Contingency management interventions, which provide tangible incentives in exchange for engaging in treatment and maintaining abstinence, have also been shown to be effective. Motivational Incentives for Enhancing Drug Abuse Recovery (MIEDAR), an incentive-based method for promoting cocaine and methamphetamine abstinence, has demonstrated efficacy among methamphetamine misusers through NIDA's National Drug Abuse Clinical Trials Network.[35]

Although medications have proven effective in treating some substance use disorders, there are currently no medications that counteract the specific effects of methamphetamine or that prolong abstinence from and reduce the misuse of methamphetamine by an individual addicted to the drug.

What treatments are under development for methamphetamine use and addiction?

Pharmacological Treatments

There are currently no medications that counteract the specific effects of methamphetamine or that prolong abstinence from and reduce the use of methamphetamine by an individual addicted to the drug. NIDA has made research on the development of medications to treat addiction to stimulants and other drugs a priority, and NIDA-funded researchers are investigating a number of pharmacological approaches for treating methamphetamine use disorder.

When developing drug treatments, researchers typically examine the impact of potential medications that have neurobiological effects that may counter the known physiological consequences of chronic methamphetamine use. They may also test medications that have shown promise in treating other addictions or other psychiatric disorders. The following targets and strategies have shown promise in animal or human studies related to methamphetamine use disorder:[15,16]

The neuroimmune system: Chronic methamphetamine use is associated with activation of microglia, cells that mediate inflammation in the central nervous system. Drugs like ibudilast and minocycline are being studied for their capacity to inhibit activation of microglia.

Cognitive enhancement: Chronic methamphetamine use is also associated with cognitive problems, such as impaired decision-making and impaired behavioral inhibition. Several drugs are under investigation for their potential to improve cognition in people who use

methamphetamine.

Dopamine agonist treatment: Medications based on activation of the same receptors targeted by an addictive drug are effective in treating other addictions, such as the use of methadone or buprenorphine to treat opioid use disorder and the use of nicotine replacement to assist smoking cessation. Since methamphetamine targets the dopamine system, some stimulant medications that activate dopamine receptors (agonists) and that are often used to treat attention-deficit hyperactivity disorder (ADHD) are being investigated as potential medications to treat methamphetamine use disorder.

Other monoamine (serotonin, norepinephrine, dopamine) targets: Methamphetamine withdrawal symptoms are similar to depression, leading researchers to investigate the utility of antidepressants that act on the serotonin and norepinephrine systems for methamphetamine use disorder. Antipsychotic medications also act on the dopamine system and may have promise for ameliorating the effects of chronic methamphetamine use.

The opioid system: The euphoric effects of addictive drugs likely involve the opioid system. Candidate medications in this category include the opioid antagonist naltrexone (currently being studied in combination with the antidepressant bupropion) and the opioid partial agonist buprenorphine.

GABA and glutamate systems: Several medications targeting disruptions in the balance of excitation and inhibition (mediated by the neurotransmitters GABA and glutamate) are being investigated to treat methamphetamine use disorder.

Hormones: The hormones cholecystokinin-8 and oxytocin have both shown promise in reducing the rewarding properties of methamphetamine in animals.

Nonpharmacological Treatments

Nonpharmacological treatments do not involve use of medications. Such therapies may instill behavioral changes by altering brain activity patterns (TMS), helping people learn how to monitor and control brain activity to curb symptoms of addiction (neurofeedback), or keeping drugs out of the brain (vaccines). Although further research is needed on these approaches, they may provide additional options for treatment providers and patients.

Transcranial Magnetic Stimulation: TMS is a noninvasive method of stimulating the brain using magnetic pulses for therapeutic purposes. Researchers are studying this approach as a treatment for substance use disorders, but this work is in very early stages.[52]

Neurofeedback: Neurofeedback (also called neurotherapy or neurobiofeedback) is a type of biofeedback that uses real-time displays of brain activity—most commonly electroencephalography—to teach people how to regulate their own brain function. In one study, neurofeedback to treatment for methamphetamine use disorder reduced addiction severity and improved mental health and overall quality of life.[53]

Vaccines and antibodies: Methamphetamine vaccines, which recruit the body's immune system to keep the drug from entering the brain, are currently being tested in animals,[54] and a human clinical trial is currently underway to test an immunologic agent called a monoclonal antibody, which binds to methamphetamine and neutralizes it before it can exert its effects.

Where can I get further information about methamphetamine?

To learn more about methamphetamine and other drugs of abuse, visit the NIDA Web site at drugabuse.gov or contact the *DrugPubs* Research Dissemination Center at 877-NIDA-NIH (877-643-2644; TTY/TDD: 240-645-0228) or online at drugpubs.drugabuse.gov.

What's on the NIDA Web Site

- Information on drugs of abuse and related health consequences
- NIDA publications, news, and events
- Resources for health care professionals
- Funding information (including program announcements and deadlines)
- International activities
- Links to related Web sites (access to websites of many other organizations in the field)

NIDA Web Sites

- drugabuse.gov
- teens.drugabuse.gov

Other Resources

Information on drug misuse and other mental disorders is also available through these websites:

- National Institute of Mental Health: *nimh.nih.gov*
- National Institute on Alcohol Abuse and Alcoholism: *niaaa.nih.gov*
- Substance Abuse and Mental Health Services Administration Publications Ordering: *store.samhsa.gov*

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